UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,333	05/06/1999	JAN VIJG		3313

7590 10/21/2002

ROBERT H RINES
RINES AND RINES
ATTORNEYS AT LAW
81 NORTH STATE STREET
CONCORD, NH 03301

EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Application No.	Applicant(s)
09/306,333	Jan Vijg
Examiner	**Art Unit**
Jehanne Souaya	1634

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 2, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4-14* is/are pending in the application.

4a) Of the above, claim(s) *7-9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4-6 and 10-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on August 2, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/306,333 is acceptable and a CPA has been established. An action on the CPA follows.

2. Currently, claims 4-14 are pending in the instant application. Claims 7-9 have been withdrawn from consideration as being drawn to a non elected invention. Claims 4-6 and 10-14 are under consideration and an action on the merits of said claims under consideration follows. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. It is noted that the response mailed August 2, 2002 states that SEQ ID NOS 121 and 122 should be deleted from the clamping sequence listing and that a corrected copy of the clamping

sequence listing was attached. Firstly, it is noted that there is no section in the specification titled "clamping sequence listing". Secondly, it is noted that only a correction of table 4, deleting reference to SEQ ID NOS 121 and 122 was attached to the response, however no attachment labeled "clamping sequence listing" has been provided. Further, it is noted that the sequence listing to the specification still recites the sequences of SEQ ID NOS 121 and 122, and that such can only be deleted by filing 1) a new written version with the subject matter in question deleted, and 2) a computer readable version of the new written version of the sequence listing, as well as 3) a statement asserting that no new matter is included. The examiner cannot delete the subject matter from the computer readable version already on file. Appropriate correction is required. See MPEP § 2426.

Specification

5. The amendment filed October 25, 2000 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Newly added table 4 recites SEQ ID NOS not identified in the original specification. The original specification listed a clamp name next to a specific primer sequence (see p. 10 of specification as originally filed), however neither a SEQ ID NO nor an actual sequence was taught or defined corresponding to a clamp name. One of ordinary skill in the art would not have been able to deduce the specific nucleic acid sequence of

these clamps (GC 3, GC 13, GC 12, etc) given the disclosure in the specification as originally filed, or from the prior art. Neither the specification, nor the prior art define which sequence corresponds to which clamp nor which primer or exon sequence it was paired with. Consequently, the pairing of SEQ ID NOS 27, 29-32 with an exon or primer from table 4 constitutes new matter.

The amendment filed August 2, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Claim 10 recites "linking sequences" and claim 11 recites "non detecting gels" which are not taught in the specification.

Applicant is required to cancel the new matter in the reply to this Office action.

Response to Arguments

The response filed August 2, 2002 asserts that the "new matter" objected to in paragraph 6 of the previous office action has been canceled. However, upon thorough review of the response, it is noted that newly amended table 4 continues to pair a particular SEQ ID NO clamping sequence with a primer pair and that such pairing introduces new matter into the specification, as explained above and in the previous office action. Applicant is required to cancel the new matter in the reply to this Office action.

Claim Objections

6. Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 is dependent on claim 10, however the limitation of claim 12, wherein an eleventh exon fragment has been split 16 times to produce said exon fragments numbered 11.1F and R through 11.16 F and R is already a limitation of claim 10, that is, due to the recitation in claim 10 : "...11.1F and R though 11.16 F and R, using primer sequence pairs SEQ ID NOS 47 and 48 through SEQ ID NOS 77 and 78" can only result in 16 fragments due to the number of primer pairs (16) used this particular step of claim 10, therefore newly added claim 12 does not further limit claim 10. It is noted that claim 10 was rejected under 35 USC 112/2nd paragraph because it was unclear if all the different primer pairs for short distance PCR are used in the method or if they are to be used in the alternative, if the latter is the case, claim 10 should be amended to reflect such so that claim 12 would further limit claim 10.

Claim Rejections - 35 USC § 112

New Matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10 and 11 recite the limitations "linking sequences" and "non detecting gels" which are not supported by the originally filed specification or claims.

Indefinite

9. Claims 4-6 and 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 4 is indefinite as it cannot be determined if the 'test kits' contain a single primer pair or a combination of primer pairs.

B) Claim 10 is indefinite because it is unclear if the method is carried out using all of the appropriate primers for long distance follow by only a specific set of primers for short distance PCR, or if the method is carried out using all of the recited primer sequences. For example, does the method encompass using SEQ ID NOS 37-46 for long distance followed by only a specific set of primer pairs for short distance PCR, such as those for producing fragments 11.1-11.16, but not 2-10 and 12-24? Furthermore, the preamble states that the method is drawn to 'detecting mutations [more than one] in BRCA1 genes', however, the final positive process step recites

"subjecting the second set of amplification products to two dimensional gel electrophoresis to produce a characteristic spot pattern for a specific mutation [single] in the BRCA1 gene. Therefore, it is further unclear if the method is drawn to detecting multiple mutations or a specific single mutation.

C) Claim 10 is indefinite as it cannot be determined if some positive process steps of the method are redundant or if each step denotes a positive process step. For example, lines 2-5 recite the step of amplifying a test sample by long distance PCR with specific primers, however, line 5 then recites an additional step of "producing a first set of amplification products". Is this first set of amplification products the same as those that would be produced from the positive process step of lines 2-5 or does it denote a separate amplification reaction. If the former is the case, this rejection can be overcome by reciting instead: "amplifying a test sample containing nucleotide sequences by long distance PCR, using primer pair sequences SEQ ID NOS 37 and 38, 39 and 40, 41 and 42, 43 and 44, and 45 and 46 to produce a first set of amplification products with exon fragments numbered 10-11, 12-13, 14-17, 18-20, and 21-24 respectively". It is further noted that the claim is confusing as to which steps actually denote a new positive process, as some processes seem to be separated by a semicolon (;), while others are separated by only a comma (,), thus it is unclear if such inconsistent use is in error or if they are meant to indicate steps within steps. For example, it cannot be determined if the step of "with claiming and linking sequences therefore" in line 11 is meant to denote a step of using the GC clamps and linking sequences *after* the step of short distance PCR, that is during the electrophoresis step, *in*

between the short distance PCR step and the electrophoresis step, or *during* the short distance PCR step. Applicant is advised to denote each separate positive process step in the method by a separate letter such as "a)" and "b)" corresponding to to a single positive step, and steps within steps as, for example, more than one step occurring sequentially in step to) as "I)" and "(ii)".

D) The recitation of 'the BRCA1 gene' lacks proper antecedent basis, as it is unclear which of the "BRCA1 *genes*" (recited in lines 1 and 2 of claim 10) it refers to.

E) Claim 10 is indefinite as it is unclear which exon fragments are being referred to. The claim specifically recites for example, "exon fragments 11.1F and R", however the specification does not support two different exon fragments "11.1F" and "11.1R". The specification uses the "F" and "R" recitation when referring to primers, not to exon fragments. Therefore, it is unclear which exon fragments the claim refers to. For example, do SEQ ID NOS 47 and 48 refer to primer pairs for exon fragment 11.1F, and SEQ ID NOS 49 and 50 refer to primer pairs for exon fragment 11.1R?

F) Claim 10 is indefinite in the recitation of "capable" in line 2 as it is unclear if the primers of the first step are actually used to amplify the entire coding sequence of BRCA1 genes, or if they are only 'capably' of such, but are not used. Further, are these PCR primers the same primer pair sequences of SEQ ID NOS 37-46?

G) Claim 11 is indefinite in the recitation of 'non-detecting' gels. The specification does not define this term, nor is this a term readily used in the art, therefore it cannot be determined

what is meant by "non detecting gels" and consequently, the metes and bounds of the claim are unclear.

H) Claims 12-14 are indefinite as it cannot be determined where in the method of claim 10, these steps are to be carried out. See section C above.

Claim Rejections - 35 USC § 103

10. Claims 4-6, 10-11, and newly added claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijg, Jan (WO 96/39535 referred to as VIjg) in view of Vijg et al (Vijg II, US Patent 6,007,231), Park et al (US Patent 5,948,697) and Liskay et al (US Patent 5,922,855) and further in view of Ahern, Holly (The Scientist, vol. 9, July 24, 2995, from the Internet, pages 1-5).

Vijg teaches a method for diagnostic testing of DNA using PCR amplification followed by electrophoretic separation (TDGE) of the resulting fragments to detect possible gene variants of mutational defects (see abstract), specifically in the retinoblastoma gene. Vijg teaches that with the method, it is possible to test an individual at any time for inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases (see p. 3, lines 1-8). The method taught by Vijg comprises amplifying regions of target DNA, usually protein coding regions (exons), by PCR (see p. 6, lines 20-23) using primers which have been positioned to cover the exons. Vijg teaches that these amplification reactions are conducted separately, eg., if 27 exons in a gene are being analyzed, then 27 separate PCR reactions must be conducted, but also teaches that it is usually possible to conduct a few PCR

reactions together in one tube (see p. 7, first para). Vijg then teaches that primers for short PCR are positioned such that a) the desired target sequences should be covered by amplicons of between 100 and 600 bp, b) amplicons should have optimal melting behavior, ie: consist of one lowest melting domain in addition to the GC-clamp attached to one of the primers, c) optimal amplicon distribution over a 2D gel, and d) similar reaction kinetics (See table 1, p. 13). Vijg then teaches that the PCR conditions are set up separately for each primer set with the long-PCR products as template for the short PCR and that multiplex co-amplification conditions are developed by grouping primer sets and adjusting reaction components. After the PCR, Vijg teaches that the mixture of fragments are subjected to 2-D electrophoresis in a denaturing gradient gel(see p. 16, lines 16-20) (TDGE based on DGGE). Vijg specifically teaches ways of improving TDGE (pp 6-9) and further teaches that the method is new and improved (p. 10, line 18), has promise for becoming a cost effective and widely accepted DNA diagnostic system (p. 5, lines 21-22), and is efficient and accurate in examining mutations (p. 2, lines 5-6).

Although Vijg does not teach testing gene sequences of the BRCA1 gene, nor the specific primer pairs of the presently claimed invention, Vijg does teach the use of the method to generally detect sequence mutations in any gene, provided the nucleotide sequence of the gene is known, and specifically teaches analyzing the retinoblastoma gene. The BRCA1 gene sequence was well known in the art at the time of the invention, as was the link between mutations in this gene in different types of cancer (BRCA1 in breast and ovarian cancer). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the

method taught by Vijg to detect mutations in the BRCA1 gene as Vijg teaches the usefulness of the method in detecting inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases. The ordinary artisan would have been motivated to use the method taught by Vijg to detect mutations in BRCA1 as both Liskay et al and Park et al teach mutations in the BRCA1 gene and its link to cancer. The ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, primers could be generated that would both successfully amplify the necessary coding regions of the BRCA1 gene and provide characteristic 2-D spot patterns for certain mutations as Vijg and Vijg II both teach in extensive detail (see pp 7-10, 18-19 of Vijg; and col.2, col.6, col.9, and claim 1 of Vijg II) how to prepare primers that would be successful in the method taught by Vijg given a known gene sequence and using long distance and short distance multiplex PCR. Using the references of Vijg and Vijg II, the ordinary artisan would have been motivated to develop primer sequences using the directions of Vijg and routine experimental manipulation for use in the method of Vijg in view of Vijg II, Park, and Liskay. Such primers are considered functionally equivalent to the primers of the present invention, absent evidence to the contrary, because the disclosure of Vijg and Vijg II teach in specific detail how to pick specific primer pairs, how to determine appropriate lengths for amplification products, and how to use GC clamping sequences to reliably detect genetic mutations in already known genes. The ordinary artisan would have been motivated to use the method of Vijg to detect mutations in the BRCA1 gene because Vijg teaches that the method can be used to reliably detect genetic mutations and

both Liskay and Park teach that BRCA1 gene mutations are linked to cancer. Although Vijg in view of Vijg II, Park and Liskay, do not teach primer pairs in kit format, Ahern teaches that premade reagents and kits are convenient and save time (p. 4, 2nd para). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package primers for amplification and detection of the BRCA1 gene in kit format, along with appropriate gel or gel materials and reagents for use in the method as taught by Vijg, for the purpose of providing premade kits to practice the method of Vijg in view of Vijg II, Park, and Liskay for the obvious improvement of having the reagents in a convenient format that would save the ordinary artisan time in practicing the method of Vijg in view of Vijg II, Park, and Liskay.

With regard to claim 12, the recitation of "split 16 times" has been interpreted to encompass using primer pairs to produce 16 fragments of the eleventh exon. It would been prima facie obvious to the ordinary artisan to "split" large exons into smaller fragments as Vijg specifically teaches at p. 19, step a of "multiplex short PCR" that desired target sequences should be covered by amplicons between 100 and 600 base pairs. With regard to claim 13, which recites "a pair of clamping sequences" it is noted that Vijg II teaches (claim 2 of Vijg II) a method in which, in the event of overlap clustering of PCR fragments along the one dimension, changing the position of primers and/or changing the size of the GC clamp sequences. Vijg II further teaches (claim 5 of Vijg II) a method in which varying of the length of the GC clamp letter sequence is effected by adding a second GC clamp sequence. Thus Vijg II expressly teaches

using two clamping sequences in the event of overlap clustering of PCR fragments. It is further noted that Vijg teaches that GC clamps are essential to guarantee the highest sensitivity to detect mutations in the denaturing gradient gel. Thus, it was known in the art at the time of the invention that using a GC clamp was important for highest sensitivity. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to provide a second GC clamp for the purposes of increasing sensitivity as it was known in the art that a GC clamp improved sensitivity of denaturing gradient gels. The courts have held that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) [see MPEP 2144.06]. See further *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) [MPEP 2144.06 VI.B] regarding duplication of parts.

Response to Arguments

The amendment and arguments, as well as the reference entitled "A highly accurate, low cost test for BRCA1 mutations" (J Med Genet. Vol 36, pp 747-753, 1999) by Orsouw et al have been thoroughly reviewed but were found unpersuasive to place the instant application in condition for allowance.

Firstly, the response asserts that the "Vijg et al paper", which the examiner assumes is meant to signify the Orsouw et al reference, reports that the particular specific now-claimed primers has produced "unexpected" and "improved" results. This argument as well as the Orsouw reference have been thoroughly reviewed but were not found persuasive. The Orsouw et al reference teaches a method comprising long distance and short distance multiplex PCR using specific primer pairs and GC clamps, and subsequently analyzing amplified sequences using TDGE to detect mutations in the BRCA1 gene. However, Vijg also teaches a method comprising long distance and short distance multiplex PCR using specific primer pairs and GC clamps, and subsequently analyzing amplified sequences using TDGE to detect mutations. It is unclear, therefore, what the results of Orsouw are "unexpected" or "improved" over. Given the prior teaching of Vijg and Vijg II, the ordinary artisan would have had a reasonable expectation of success that using the method of Vijg in view of Vijg II, Park and Liskay, and the specific steps taught by Vijg and Vijg II, would have allowed an ordinary artisan to reliably detect mutations in any known gene, including the BRCA1 gene. As the BRCA1 gene was known in the art at the time of the invention, the ordinary artisan would have had a reasonable expectation of success that mutations in this gene could also be reliably detected using the general method taught by Vijg because Vijg teaches that such TDGE method is efficient and accurate in examining mutations (p. 2, lines 5-6). Although the combined method of Vijg in view of Vijg II, Park and Liskay does not teach the sequences of the primer pairs of the claimed methods and kits, Vijg and Vijg II teach a general method in specific detail for obtaining specific PCR primer pairs, the use

of long distance and short distance multiplex PCR, appropriate target sequence lengths, and the use of GC clamps, such that the ordinary artisan would have been able to obtain primer pairs that are considered functionally equivalent to the sequences of the presently claimed invention, absent evidence to the contrary.

The response states that the paper at the bottom of page 747 and pages 748 and 749 more fully detail the PCR primer and amplification preparation disclosed in the originally filed specification at pages 3 and 4. Further, the response asserts that Fig I of the paper (p 748) and Figure 2 (page 749) are identical to the left hand schematic chart and right hand photograph of original Fig 1B, which applicant has submitted because of the Office comment that the figures are unclear. The newly submitted figures have been thoroughly reviewed, however it is unclear how these figures show an "improved" and "unexpected" result as no basis for comparison has been provided by the response or the specification. It is unclear why, further, the Orsouw et al reference does not teach why, one of ordinary skill in the art, armed with the teachings of Vijg and Vijg II, would not expect such clear resolution and reliability from a method which uses the steps taught by Vijg and Vijg II, albeit with a different gene (it is noted that Vijg and Vijg II generally teach how to take a known gene and carry out long and short multiplex PCR, using appropriate primer pairs to amplify exons, and target sequences between 100 and 600 base pairs, and using GC clamps, -pages 3-10 of Vijg- and Vijg teaches that the general method can be used to provide "efficient and accurate examination for mutations", see p. 2 of Vijg, lines 5 and 6).

The response asserts that the abstract of the Orsouw paper teaches that 5 additional mutations were identified that previously escaped detection as well as 15 different polymorphic variants. However, as stated above, given the teachings of Vijg and Vijg II, the ordinary artisan would have expected that the method of Vijg in view of Vijg II, Park and Liskay would provide accurate and efficient examination of mutations of the BRCA1 gene or any known gene since Vijg teaches that the method provides "efficient and accurate examination for mutations", see p. 2 of Vijg, lines 5 and 6. The Orsouw paper states at page 750 that the sensitivity and specificity of the test taught by Orsouw was determined by comparing such a method which previously screened 60 DNA samples for BRCA1 mutations using the protein truncation test alone or in combination with partial nucleotide sequencing. Such sensitivity and specificity testing, however, does not show "unexpected" or "improved" results over the general TDGE method taught by Vijg which involves taking a known gene and carrying out long and short multiplex PCR, using appropriate primer pairs to amplify exons, and target sequences between 100 and 600 base pairs, and using GC clamps, to provide "efficient and accurate examination for mutations"(see p. 2 of Vijg, lines 5 and 6).

With regard to the assertion at page 5 of the response "Apart from the 'highly accurate low-cost test for BRCA1 mutations' produced for the first time by the invention (*and certainly not in the earlier cited work of Vijg*, [emphasis added])", one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

11. No claims are allowable over the cited prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
October 16, 2002